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Research ethics

Guidelines to aid ethical committees considering research involving children

The British Paediatric Association set up in 1978 a Working Party on Ethics of Research in Children (members Professor F Cockburn, Professor J A Dudgeon, Dr D M T Gairdner, Dr A D M Jackson). The following *Guidelines to aid ethical committees considering research involving children**, proposed by the Working Party have been accepted by the Council of the BPA.

These guidelines presume that four premises are accepted.

That research involving children is important for the benefit of all children and should be supported and encouraged, and conducted in an ethical manner.

That research should never be done on children if the same investigation could be done on adults.

That research which involves a child and is of no benefit to that child (non-therapeutic research), is not necessarily either unethical or illegal.[1]

That the degree of benefit resulting from a research should be assessed in relation to the risk of disturbance, discomfort, or pain—the 'Risk/Benefit ratio'.

Defining 'Risk'

Risk, in this context, means the risk of causing physical disturbance, discomfort or pain, or psychological disturbance to the child or his parents, rather than the risk of serious harm, which no ethical committee would countenance in any case.

Negligible Risk. Risk less than that run in everyday life.

Minimal Risk. Risk questionably greater than negligible.

More than Minimal Risk.

Defining 'Benefit'

Nontherapeutic research.

(a) The procedure is of no benefit to the subject but may benefit the health and welfare of other children or adults. A special case, but an important one, is if the subject suffers from a disorder and the research aims to benefit others suffering from a similar disorder.

(b) The procedure is of no benefit to the subject but may add to basic biological knowledge e.g. normal values; ageing.

Therapeutic research. The procedure is of potential benefit to the subject.

Applying the Risk/Benefit principle in nontherapeutic research

Procedures requiring ethical judgements are usually those which are without benefit to the subject—'nontherapeutic research'. Most such procedures will fall into one of the following three categories.

1. The procedure is either (a) part of the ordinary care of the infant or child (weighing, measuring, feeding), or (b) involves the noninvasive collection of samples (e.g. urine, faeces, saliva, hair, or nail clippings, or, at birth, cord blood or placental tissue).

Risk is here likely to be *Negligible*. For example, test weighing a breast-fed baby, as part of a study aimed to promote breast feeding.

2. The procedure involves invasive collection of samples (e.g. blood, cerebrospinal fluid, biopsy

*A *child* in this context is taken to include the infant from the time of birth (but not the fetus). Thereafter, an individual remains a minor until 18. The Family Law Reform Act (1969) provides that a minor who has attained the age of 16 has capacity to consent to surgical, medical, or dental treatment (which 'includes any procedure undertaken for the purpose of diagnosis . . . and applies to any procedure . . . which is ancillary to any treatment as it applies to that treatment'). This statute does not deal with consent for other procedures, e.g. nontherapeutic research, and therefore the general law applies to all minors until 18. Such law does not recognise any 'age of consent', for capacity to consent depends on the child's intellectual capability and the complexity of the procedure; age is simply one factor to be taken into account.[2]

tissue) taken from a child who is undergoing treatment. The sample used for research may be (a) an additional amount to that required on clinical grounds; or (b) not an ordinary part of the child's treatment (e.g. collection of biopsy material during a surgical operation).

Risk in (a) might be either *Negligible* or *Minimal*: (b) might be *Negligible*, *Minimal*, or *More than Minimal*.

Examples. In cystic fibrosis, a research might be considered reasonable which involved an affected child having a sweat test that needed twice as much sweat as required for purely diagnostic purposes. The added discomfort to the child might be assessed as *Negligible*. If in addition a venepuncture was required, this might be judged to put the risk of discomfort and pain into the *Minimal Risk* category. But the potential benefit to other child sufferers from this common and serious disease might be deemed such as to make the Risk/Benefit ratio acceptable.

During the course of an operation for hernia, a fragment of skin from the incision might be required for a research involving tissue culture. The *Risk* could be judged *Negligible*, so that even if the research was not expected to have any direct clinical benefit but only to add to basic biological knowledge, it might be acceptable.

During the course of an abdominal operation, a renal biopsy might be taken for research purposes. The *Risk* here would be judged *More than Minimal* and the *Benefit* would have to be very large to justify it. But suppose the research aimed to resolve the problem of rejection of transplanted kidneys, with resulting lifesaving consequences both for children and adults with renal failure, this might be considered a *Benefit* of sufficient magnitude to justify the risk.

3. The procedure is quite apart from the necessary care or treatment of the child. For example, blood sampling; passage of oesophageal tube for pressure recording; application of face mask for respiration studies; placement of infant in plethysmograph chamber for thermal or respiratory studies; needle biopsy of skin or fat; or *x*-ray or isotope studies (see below).

The *Risk* might be *Negligible*, *Minimal*, or *More than Minimal*. The *Benefit*, as defined above in relation to 'nontherapeutic research,' may fall within either the Definition (a) or (b). If it comes under Definition (a), the *Risk* should, to be acceptable, probably be either *Negligible* or *Minimal*.

If the *Benefit* comes under Definition (b) the *Risk* should be *Negligible*.

Examples. In thalassaemia, a common and lethal disease, progress might depend on taking blood specimens from both affected and unaffected children. The *Benefit* could be assessed as great, so justifying the *Risk* of causing *More than Minimal* discomfort or pain to the children.

Many diabetic children will develop blindness or other severe eye complications in adult life. A research aimed at eventually learning how to prevent this might require several glucose tolerance tests to be done on a diabetic child, not for his own benefit but to the benefit of other diabetic children. The *Risk* of discomfort or pain to that child would be assessed as *More than Minimal*, but might nevertheless be justified by the potential *Benefit*.

The physiology of the initiation of breathing by the baby at birth is poorly understood, and is of clinical importance because some babies fail to breathe. A study of normal newborn babies' first breath, using a face mask, may be judged to cause *Minimal Risk* with a justifiable Risk/Benefit ratio.

Applying the Risk/Benefit principle in therapeutic research

Therapeutic research offers potential benefit to the subject. It includes not only trials of new drugs or procedures but also trials of therapies which, though perhaps widely applied, are yet of unproved value. The Risk/Benefit principle may still be applicable, the potential *Benefit* as well as the *Risk* relating to the individual subject.

In general, ethical principles in therapeutic research involving children do not usually differ from those applying to adults, except that the age of the subject will often mean that parental understanding and agreement will be required.

In the common type of experiment where two therapies are compared in a controlled trial, two ethical questions are likely to arise.

1. Is the research necessary? For instance, conventional treatment of a febrile convulsion in a child includes drastic cooling. A research project might question this form of management and entail a controlled trial. An ethical committee might consider it probable that data already existed enabling the question to be answered. The committee might therefore require the researcher first to provide evidence that the world literature had been effectively searched.

2. Is the design of the trial such that a statistically significant result will emerge with the use of a minimal number of subjects and in a minimum period? Since one set of children will receive what may eventually turn out to be an inferior therapy, it is ethically imperative that this question be answered in the affirmative.

Examples. Current research in treating leukaemia

in children often means comparing two different drug regimens. Since both sets of children receive therapies currently considered acceptable, ethical considerations are mainly confined to ensuring that the design of the trial is statistically sound.

A controlled trial of hyposensitising injections of allergens in asthmatic children differs from the foregoing example in that some children (the controls) receive injections of inactive material. This might at first sight seem ethically questionable. However, the following consideration may lead to such a trial being judged acceptable. Until the result of the trial is known the children in either the treatment or the control group have a chance of gaining an advantage. The active therapy may prove superior and those in the treatment group gain an advantage. If, however, there are unpleasant or harmful side effects from the active therapy, the control group will have gained some advantage by not being exposed to those side effects.

X-rays and isotopes

An authoritative pronouncement on the ethical propriety of irradiating children (i.e. the use of *x*-rays or isotopes) for research purposes has recently been given by the International Commission on Radiological Protection.[3] It states that 'the irradiation, for the purposes of such studies (i.e. of no direct benefit to the subject) of children and other persons regarded as being incapable of giving their true consent should only be undertaken if the expected radiation is low (e.g. of the order of one-10th of the dose-equivalent limits applicable to individual members of the public) and if valid approval has been given by those legally responsible for such persons.'

This means, in common parlance, that exposure to *x*-rays could be justifiable where the dosage was comparable to the normal variation in natural irradiation received by, say, individuals living in two different parts of the British Isles. In fact, using modern equipment, a single radiograph might fall well within such dosage limits, and thus be classifiable as a *Negligible Risk*.

Parental permission and co-operation. Agreement by the child

Parental (or guardian's) permission should normally be obtained—with rare exceptions such as the comparison of two treatments for some emergency condition—after explaining as fully as possible the nature of the procedure. Whether or not this should be a signed, witnessed declaration remains debatable. It is an advantage if the parents can be present during the procedure. Although the law in Britain does not recognise an 'age of consent', children much younger than 16 often have enough understanding to collaborate altruistically in a project.

New drugs: new immunisation procedures

In general these should first be tested on animals, then on adult volunteers, then on older children able to take part voluntarily in the research, and only then on younger children. However, there are instances where this sequence might be inappropriate; for instance in the development of a vaccine against respiratory syncytial virus where few uninfected subjects may be available above the age of infancy.

References

1. Dworkin G. Legality of consent to nontherapeutic medical research on infants and young children. *Arch Dis Child* 1978; **53**: 443–6.
2. Skegg P D G. English law relating to experimentation on children. *Lancet* 1977; **2**: 754–5.
3. International Commission on Radiological Protection. *Ann Int Commis Radiol Protect* 1977; **1**: No. 3, 37.

British Paediatric Association

Standing Ethics Advisory Committee

(1) The British Paediatric Association has set up a Standing Ethics Advisory Committee. The function of this Committee will be to offer advice on the ethics of research projects involving children.

(2) The Committee will respond to requests for advice from individuals planning research projects, from local ethical Committees, or from editors of journals but its opinions will not be binding. Approval of research projects must remain the responsibility of statutory local ethical committees.

(3) The Committee will base its opinions on guidelines drawn up by the British Paediatric Association and if it is consulted often enough it will in time establish some uniformity of policy for research in children throughout the country.